00:00 Sarah Crespi: This week's episode is brought you in part by Lego Technic. Lego Technic isn't just another Lego set with bricks, it's real life advanced building. Some sets have interconnecting rods, working gears, even real electric motors.

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00:46 SC: Welcome to the Science Podcasts for September 14th 2018. I'm Sarah Crespi. On this week's show, I talk with science writer, Carol Cruzan Morton about the sexual awakening of the strawberry. In the last million years or so, some species have divided into two sexes, giving researchers new insight into making sex chromosomes.

01:08 SC: And Meagan Cantwell talks to staff writer Jon Cohen about how to conduct Zika vaccine trials without Zika. Some researchers are looking to give people the virus in order to test the vaccine.

01:23 SC: Strawberries appear to have the youngest sex chromosomes. Back in the day, some few million years ago, strawberries were like most flowering plants. They reproduced all in one package, they self-themselves, if you will. But at some point, since then, some kinds of strawberries divided into two sexes. Science writer Carol Cruzan Morton is here to talk about that moment, the sexual awakening of the strawberry. Hi, Carol.

01:51 Carol Cruzan Morton: Hi, Sarah.

01:52 SC: That's a really complicated introduction to the idea that there are strawberry species that have different sexes. What does it actually mean for a strawberry plant to have two sexes in its species?

02:02 CM: So for a strawberry plant to have two sexes means that you need a plant of each sex to make the strawberries. There's actually a story about this, famous botanist Carl Linnaeus originally classified strawberries incorrectly as hermaphrodites or having one plant with both sexes in it, and then in the 1800s, early 1800s, these farmers in Ohio are having a really hard time growing strawberries, and it turned out that the strawberries they were growing had two sexes, and they were only planting one of the sexes, and without the other they couldn't make little strawberries fruits.

[chuckle]

02:43 SC: So there's no reproduction. Once you have two sexes, you have to have them both to get offspring.
02:48 CM: Yes, once you have two sexes, and the strawberries are very early in that stage. So the researchers wanted to know well how... Why would a strawberry even break into two sexes, 'cause all of a sudden that complicates the game when you're rooted in the ground, and it's hard enough to find a mate if you have two legs. [chuckle]

03:08 SC: Right. And here you are, you're sitting there and now you gotta find a partner. What are the advantages? What do they think that that might be behind this?

03:17 CM: That's the big question now. So that's what they want to know. How in the world would this make life better for strawberries?

03:24 SC: Yeah, and what they wanted to do to find that out was to start out with what genes... What parts of their genome are doing this? But that wasn't easy to do at all. Why was it so difficult to figure out what was giving the strawberries its separate sexes?

03:40 CM: These days most scientists are studying strawberries to make a better barrier, a more disease-resistant plant. So this study rose just from curiosity about how the two sexes evolved in the first place. So they started with wild strawberries and they used classic cross-pollination and genetic mapping techniques. And they found in an east coast version of a wild strawberry, their first evidence of male and female sex-determining regions on one chromosome and that was about 10 years ago, that was their first big struck of luck, and then they looked at another strawberry on the other coast. It's a closely related Oregon beach strawberry. And they kind of were surprised, they found a genetic region that appeared to determine the different sexes in a different place on a different chromosome, and then a third study showed yet a third location on yet another chromosome.

04:45 SC: That makes things very complicated. I know strawberries have a lot of chromosomes, but it seems surprising that this sex-determining region would keep moving around and what the researchers did next was go to the strawberry genome project and worked together with them to figure this out. What did they find once they teamed up?

05:05 CM: In fact the researchers were part of the strawberry genome project, and they have this conversation about these different sex determining region and these three different varieties. And so they decided to take advantage of the now finished strawberry genome project, and sequenced 60 strawberry plants, and it was kind of a brute force approach.

05:31 CM: So the researchers sequenced 60 plants evenly divided between males and females. It was like they had 60 jigsaw puzzles and they were able to go through computationally and say give me all the pieces that are shared by the female plants, and they pulled those out and the rest of the box, they're not touching those.

[chuckle]

05:54 SC: And what did they learn about their location?
05:56 CM: All of these pieces lived on some version of Chromosome 6. Now remember there is
eight copies of Chromosome 6. And each of the three strawberry species that they sequenced, all of
the sex determining regions were on Chromosome 6. And the plot thickens a little bit in each of the
different species, the sex determining region is on a different part of that chromosome. And so
sometime over generations, that region appears to have jumped to different spots on the
chromosome and every time it's carried neighbors with it.

06:31 CM: When it carries neighbors, it's carrying more female-specific genes and at some point,
that's gonna become a chromosome that can only be female, kind of like the Y chromosome and
people can only be male.

06:46 SC: I know genes jump around sometimes, but how common is it in the situation where you
have all these copies of the chromosomes for something to carve out a niche like this?

06:54 CM: The whole jumping gene aspect has to be worked out, even what those genes do
specifically to make a female plant female also has to be worked out. So there's a lot of work ahead
for the researchers. [chuckle]

07:10 SC: This is not the only plant that has two sexes, it's just starting down that path. What other
plants do we know of that have two sexes? How common is this?

07:19 CM: About 6% of all plants have two sexes. I'm told they tend to be more agriculturally
important crops. Asparagus have two sexes. Their Y chromosome was just worked out recently. But
sex has risen thousands of times in plants. So the story of how strawberries came to be two sexes
may end up being unique to strawberries.

07:45 SC: So is this something that is a pattern for creating a sex chromosome? Has this been seen
before?

07:51 CM: This hasn't been seen before. That's not a complete surprise because sex has evolved
apparently hundreds or thousands of different times in plants. In the few plants that have been
studied in this detail so far, each one has a different way that the sex chromosome seems to have
evolved. So there may be thousands of different ways that sex chromosomes evolve. I guess, we'll
have to stay tuned.

[chuckle]

08:21 SC: That's great. So what can we learn if we learn the strawberry sex story? What can that
help us understand about how sex arose in all different kinds of animals and plants?

08:33 CM: The X and Y chromosomes of people, mammals, lots of all these other animals, there's
little differences but they're basically the same template. They go back about 150 million years or so
to some common origin. Plants are really different. Chromosomes in people and animals evolved so
long ago. It's almost impossible to think that you might be able to look, to get a glimpse of them at a
really early stage. I know astronomers appear into these young corners of the universe to try to get
glimpses of the processes that are happening that might have explained some aspect of the origin in the universe, and it's kind of like that in plants, you can't see the start of the different sexes in people and animals but you can see that in plants, 'cause it's happening now.

09:28 SC: Thanks, Carol.

09:29 CM: Thanks, Sarah.

09:29 SC: Carol Cruzan Morton is a science writer based in Oregon. You can find the link to her story and some pictures of strawberries at sciencemag.org/podcasts. Stay tuned for an interview with Jon Cohen about Zika vaccine research. Case numbers have dropped off a cliff. How can a vaccine be validated?

[music]

09:55 SC: This week's episode is also brought to you in part by Bombas Socks. Thanks to two years of research and development and multiple improvements and design, performance, and comfort. Bombas are now officially the most comfortable socks in the history of feet. With an arch support system that provides extra support where you need it most and a cushion foot bed that's reinforced for comfort, without added bulkiness, Bombas feel like a hug around your foot.

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[music]

11:06 Meagan Cantwell: I'm Meagan Cantwell, and I'm here with Jon Cohen, a staff writer at Science, to discuss his new story on how researchers are overcoming hurdles to developing a vaccine for the Zika virus. Hey, Jon.

11:16 Jon Cohen: Hey, how you doing, Meagan?

11:17 MC: Doing well. So Zika was widely discussed in 2016 but it hasn't had as much coverage lately. Could you give a quick run-down on how it spreads and what about the virus that's so dangerous to humans?

11:28 JC: It's a mosquito-borne disease, which means that mosquitoes bite people, they get infected, then fly over to another person, bite another person, a new mosquito comes along, bites a person and it goes on from there and Zika's been around, it's been known about since 1947, but in 2016, it really exploded into a disease that's widely feared, because of an unusual thing that happens in babies. It's a brain damage called microcephaly and no one had ever seen that before.
12:00 JC: Until then, Zika had been seen as just a mild disease. You get a little fever, a little rash, but really not a frightening disease at all.

12:08 MC: Right. So in response to this birth defect in babies, they quickly started to develop vaccines and several vaccines were in development, one of which was launched by the National Institute of Allergy and Infectious Diseases. So what was their initial timeline for developing a vaccine?

12:24 JC: They rushed the vaccine through early animal and human studies, rushed in a good way. I don't mean that it was irresponsible. Zika looked like a pretty easy bug to stop. It's a virus looked like most everything worked in animal models, and so they moved forward with the vaccine that by 2017, looked like it was ready for a trial to test whether it really works in the real world.

12:51 JC: Early vaccine studies just look at safety and immune responses, but then when you get to the later stages, you put it into a place where the disease is being transmitted.

13:01 MC: And unfortunately, they ran into some problems there. Large trials are structured so that they compare the infection rate from those who get a placebo of the vaccine to those that actually receive the vaccine, so why couldn't they measure this?

13:14 JC: They selected nine countries that had active transmission of Zika and Zika petered out in each of those countries, and these were in North and South America. Basically, if there's no transmission, there's no way to really test the vaccine and see whether it works.

13:30 MC: Yeah, and Zika's disappearing act actually shouldn't come as too much of a shock. You interviewed someone, Scott Halstead, leading expert on viruses in 2016, who predicted that Zika would peter out within his quote five years max. So what was Halstead's reasoning for that?

13:47 JC: When people become infected with Zika, we think they develop lifelong immunity. In Brazil at the peak of transmission, there were about 20,000 suspected and confirmed cases every week, so it was just racing through entire populations and if you get 50%, 60% of a population with immunity to most any disease, the disease will peter out, it just can't spread. It's called herd immunity, so there likely is widespread herd immunity in South America and North American and places that were hard hit, and it's harder for that transmission cycle of mosquito to human to keep it going.

14:25 MC: If people are gaining immunity, Zika at this rate and it's slowing new infections, why is it still important for researchers to develop a vaccine for this?

14:34 JC: There's still lots of pockets around the world that have never had Zika or have only had Zika come through at low levels. Keep in mind also that there are babies being born every day even though there might be widespread immunity in, let's say, Brazil today, 10 years from now, there might be a huge population of susceptible children.
Now, they won't be of reproductive age, but go forward another 10 years, these epidemics come and go, they wax and wane.

Do you have any idea of the periodicity of the Zika virus? Do you think if it wanes it'll come back in another 50 years, or what is kind of the timeline you anticipate?

I don't think anyone knows that. And there's a lot of unpredictability, because there are pockets even in places where the virus hit big time. Take Brazil, Sao Paulo is a city of 12 million people. There are pockets in Sao Paulo where only 5% of the people have Zika Antibodies. So for whatever reason, the mosquito didn't hit certain regions of that city and that's what you're gonna find in every country in South America, and North America, there are pockets that didn't get hit.

But luckily there is still a way to test the effectiveness of the vaccine and that's through vaccinating people then intentionally infecting them with Zika virus and all of this sounds terrifying. It's been done for a variety of diseases ranging from the flu to Norovirus. The NIAID has plans to carry out this type of experiment in 2019, but what are the risks associated with a human challenge experiment for Zika?

In the case of Zika, they can minimize risk in a lot of ways. I remember it's not a dangerous disease for adults, it very rarely causes serious symptoms. One of the concerns in doing a human challenge is that there is sexual transmission, but it's from males to females.

So this study is gonna focus on women and it will compare them to women who are intentionally infected, who aren't given the vaccine, and it will be small numbers and they'll stay as in-patients in the hospital until the virus clears in their body, which takes a couple of weeks.

So human challenge experiments were proposed in 2017 but they ultimately decided not to move forward with it. What has changed in 2018 that necessitates this type of experiment?

Well, when an ethical review committee went through the details of this, the committee concluded that the risk wasn't worth the benefit because at that point in time, it appeared as though you could do field testing, real-world testing as the NIAID-sponsored trial is still trying to do.

There were, in addition to the NIAID study, Sanofi Pasteur, one of the world's largest vaccine makers had a Zika vaccine project at that time. So it looked like traditional vaccine studies could answer the question. It wasn't clear at that point in time how long sexual transmission could occur or whether it was just male to female or female to male, that's become much clearer over time that it really doesn't last that long in the body.

Back in February 2017 when the Ethics Committee wrote its report, there were some reports that thought Zika could last for six months, so that changed what's called third-party harm. I mean, imagine if somebody who doesn't participate in a challenge study gets infected from someone who did participate, ethically, how can you do that? They didn't decide to take part in this. So that was the concern at the time but the equation's changed.
**18:08 JC:** Sanofi Pasteur dropped out, it ended its Zika vaccine development program. There are combination of reasons why, part of it has to do with the drop in transmission and it became unclear what the marketplace was. That factors into the big picture of the whole field and why the human challenge model gained some currency because there's less interest than there was from vaccine developers.

**18:31 MC:** When would they anticipate a commercial-ready vaccine by?

**18:34 JC:** The human challenge experiments aren't necessarily going to in and of themselves lead to a licensed vaccine. They'll contribute information with the ongoing study that's taking place in nine countries. You need safety data, you need immune response data.

**18:49 JC:** If you took that same population that was vaccinated and challenge those people, then you could combine all that information to apply for licensure, but it would probably take at least another year, would be my guess. And it's not clear that they're gonna do challenge studies with the vaccine that's being used in the NIAID-sponsored study. So it could be several years. I don't anticipate a Zika vaccine coming to market anytime soon.

**19:17 MC:** It makes it possible for them to even study the efficacy of the vaccine through these human challenge experiments.

**19:22 JC:** Yeah, that's right, and it could speed up the whole approval process. If in early 2019 or mid-2019, we know that a specific vaccine works in a challenge model, that vaccine then might be used during an outbreak, let's say, an outbreak takes place in that neighborhood in Sao Paulo I mentioned, let's say there are several million people there and you put in a vaccine that's proved itself in a challenge study, it then can prove itself in a real outbreak, and that can all happen pretty quickly. We've seen this happen with the Ebola vaccine and it's now being used twice in real-world outbreaks in Democratic Republic of Congo. It still hasn't received licensure, but it's getting a real-world test now.

**20:04 MC:** Alright, thank you so much, Jon.

**20:05 JC:** Yeah, you bet.

**20:06 MC:** Jon Cohen is a staff writer at Science. You can find a link to his story at sciencemag.org/podcasts.

**20:13 SC:** And that concludes this edition of the Science Podcasts. If you have any comments or suggestions for the show, write to us at sciencepodcast@aaas.org. You can subscribe to the show anywhere you get your podcasts or you can listen on the Science website, sciencemag.org/podcasts.

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